This is the section on clinical recruitment methods from the grant application for MGS2; procedures for MGS1 were identical except that ascertainment was based on referrals of prospective subjects with a possible affected sibling pair (SZ proband, SZ or SA sibling) in the family.

D1b. Recruitment. The sample will reflect the clinical population in the community mental health system because all individuals with appropriate diagnoses will be eligible. Non-systematic recruitment maximizes access to eligible cases. Recruitment procedures will be similar to those in the current study, with each center utilizing the methods described in its site-specific section below. Methods of contacting individual subjects are described in section E. Recruitment is typically through referral by a cliinician, a family member, confidential screening of records with subsequent contact by a clinician, or family self-referral (web or advertisement). Each PI will meet regularly with staff to supervise recruitment and selection of appropriate cases. Staff will seek referrals of subjects likely to have SZ, including subjects across the clinical spectrum – i.e., not just the most cooperative cases, which could be a bias, but also those who are sufficiently paranoid or withdrawn to require considerable skill on the part of research staff to explain the study and develop rapport. Subjects will be paid a modest honorarium ($75 for probands, $25 for parents who contribute blood specimens).

(1) Inclusion criteria for probands:

1. All subjects must give signed, informed consent.
2. Probands must have a consensus best-estimate DSM-IV diagnosis of SZ OR of schizoaffective disorder with at least six months' duration of the "A" criteria for schizophrenia.
3. Subjects must be over 18 years of age at interview, male or female.

(2) Exclusion criteria for probands:

1. Unable to give informed consent to all aspects of the study.
2. Unable to speak and be interviewed in English (to ensure validity of the interviews).
3. Psychosis is deemed secondary to substance use by the consensus diagnostic procedure because psychotic symptoms are limited to periods of likely intoxication or withdrawal, or there are persistent symptoms which are likely to be related to substance use (i.e., increasing paranoia after years of amphetamine use; symptoms limited to visual hallucinations after extensive hallucinogen use).
4. The psychotic disorder is deemed secondary to a neurological disorder such as epilepsy based on the nature and timing of symptoms. For example, non-specific, non-focal EEG abnormalities are common in SZ, but subjects with psychosis that emerged in the context of temporal lobe epilepsy would be excluded.
5. Subjects with severe mental retardation (MR). Subjects with mild MR (IQ≥55 or based on clinical and educational history) will be included, if SZ symptoms and history can be clearly established.

(3) Inclusion criteria for informants:

1. The informant should have known the subject for at least two years, be familiar with the psychiatric history, and have at least one hour of contact per week with the proband (close family members preferred).

D2. Comprehensive phenotypic assessment and diagnosis. Each potential subject will be contacted as described above and informed consent obtained (see section E). Each proband will be interviewed using the modified **Diagnostic Interview for Genetic Studies (DIGS)** and **Family History Interview for Genetic Studies (FIGS)** (Nurnberger et al., 1994), as in the first Genetics Initiative study and our current study.

(a) The **DIGS** is a semi-structured interview for studies of psychotic and mood disorders. It covers relevant history and symptoms including sections on demographic, personal and medical history, depression, mania, and substance abuse. The psychosis section covers positive,

negative and disorganized symptoms, with SAPS and SANS ratings of these domains. Modifications for the current project included skipping the anxiety and somatization sections and clarifying several items. As described in C1 we have added probes for longitudinal history of major symptoms. The DIGS typically takes 2-3 hours. All sites have extensive experience in its use and participated in reliability exercises (C1). Interviewers write a narrative that includes a description of the subject (mental status), historical summary, descriptive examples of symptoms, and explanation of "unknown" ratings; this provides descriptive data for the consensus diagnosis process. "DIGS interview" refers here to the interview, narrative report, independent review of the interview to identify missing data, errors or inconsistencies, and corrections based on this review.

(b) FIGS. The FIGS will be used (1) to obtain information about the proband; and (2) screening more briefly to determine if there is a possible family history of psychosis. To collect more extensive family history diagnoses would be time-consuming, without (in our judgment) making the case-control sample more valuable. Our recent modifications to the FIGS add items about the longitudinal course of the proband's major symptoms. The FIGS takes about 30 minutes for informants and 5-15 minutes for the proband.

(**c) Medical and other psychiatric records:** All interviewed subjects will be asked to sign requests to permit us to obtain relevant records. This can include relevant records of neuropsychiatric assessment and treatment, military and school records, and other medical records that may include information about symptoms and behavior to assist in evaluating age of onset and course of illness.

(**d) Best estimate diagnosis:** Diagnoses will be assigned by the Best Estimate Final Diagnosis (BEFD) procedure by consensus of two diagnosticians, with a third senior diagnostician resolving disagreements. This procedure requires that each of two senior research diagnosticians (M.D. or Ph.D. with research diagnostic experience) independently review all available information about the subject, including DIGS, narrative, FIGS and records. Each diagnostician assigns diagnoses using a DSM-IV criteria review form. The two diagnosticians then confer. Initial diagnosis and criteria ratings, prior to discussion, will be preserved and reported as part of the clinical database. If a disagreement is not resolved, additional interview of records information may be sought. If after this discussion there is disagreement between SZ and SA diagnoses, a third independent diagnostician will "vote." However, if one diagnostician still favors an ineligible diagnosis (such as bipolar disorder or delusional disorder), the case will be excluded. The two diagnosticians will also reach consensus ratings of age of onset, duration of illness, duration of psychosis and of mood syndromes, and presence/absence of individual DSM-IV criteria for SZ and SA disorders.

(**e) Dimensional ratings.** The LDPS has been described in C1. The SZ phenotype can be viewed as a set of dimensions of symptoms and course. The Schedule for Assessment of Positive Symptoms (SAPS) and Schedule for Assessment of Negative Symptoms (SANS) are included in the DIGS and will be rated by the interviewer to provide cross-sectional assessments. LDPS ratings will be made by one Best Estimate diagnostician per case, based on all sources of information. A rating of mode of onset (from insidious to abrupt) will be added to the LDPS and probes added to the DIGS and FIGS. We view it as a strength that a senior diagnostician rates these multiple domains on the basis of all sources of data.